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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,989	03/13/2006	Michael Kalafatis	CSU-17999	5552

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,989	KALAFATIS, MICHAEL	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,43-49,51 and 112-135* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,43-49,51 and 112-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8, 10, 43-49, 51, and 112-135 as recited in the preliminary amendment received 3/13/06 are currently pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 43-49, 51, 115, 117, 119, and 120-135 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 51, 115, 119, 127, and 135 recite compositions comprising "peptide analogues" that "mimic" various peptides, but the nature and degree of this mimicry is not particularly pointed out. It is not clear whether these claims require that the analogues have structures, functions, effects on cells or patients, or some combination thereof similar to the peptide. Clarification is required.

Claim 43 is drawn to a composition "adapted for inhibiting thrombin formation," but it is not clear what physical properties of the composition render it particularly adapted for this function. Furthermore, the source of thrombin is not clear; the claim should point out from where or from what thrombin is formed. Clarification is required. Because claims 44-49 and 51 depend from indefinite claim 43 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 117 depends from claim 116, which is drawn to a peptide that "consists of" a particular sequence (i.e., does not allow the inclusion of any other components) of

between 2 and 5 amino acids defined as being consecutive in a particular protein. However, claim 117 requires that the peptide of claim 116 "comprise" a particular 5-amino acid sequence. These transitional phrases are not compatible as utilized in these claims. Clarification is required. If claim 117 is intended to refer to the embodiment in which the peptide of claim 116 consists of the amino acid sequence DYDYQ, it should recite such.

Claims 120 and 128 are each drawn to a composition "adapted for inhibiting thrombin generation," but it is not clear what properties of these compositions render them particularly adapted for this function. Furthermore, the source of thrombin is not clear; the claim should point out from where or from what thrombin is generated. Clarification is required. Because claims 121-127 and 129-135 depend variously from indefinite claims 120 and 128 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 10, 43, 44, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Hortin (1990, *Blood* 76: 946-952; reference AM on 3/13/06 IDS). The claims are interpreted as being drawn to a peptide comprising a sequence of amino acids that is identical to a sequence of at least 2 consecutive amino acids found within a

4-amino acid region of a longer reference sequence. In some dependent claims, the peptide has a particular activity or comprises a particular sequence. Some claims are drawn to compositions comprising the peptide or compounds that mimic the peptide in some way. It is noted for the record that claim 1 is currently so broad as to encompass any peptide that contains either the sequence DY or the sequence YD along with any other amino acids in any sequence. The scope of claim 43 encompasses any peptide that contains the sequence DYDY along with any other amino acids in any sequence.

Hortin teaches that the complete sequence of human coagulation factor V (hereafter "Factor V") was known at the time of the invention and that said sequence includes the sequence DYDYQ (page 946, column 1, paragraph 2; and Figure 6 at page 950, e.g.). Hortin teaches a solution comprising Factor V (page 946, column 2, last paragraph).

M.P.E.P. § 2112 recites, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v.*

Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). In this case, the claims encompass numerous peptides, including Factor V itself. Peptides cannot be separated from their inherent properties, and since the peptide as instantly claimed is identical in structure to the prior art peptide, the two necessarily have the same properties, including those recited in claims 2-5 and 43. Claims 10 and 51 are included in this rejection because a given composition is a perfect mimic of itself in every way.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-8, 10, 43-49, 51, and 112-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hortin (1990, *Blood* 76: 946-952; reference AM on 3/13/06 IDS) taken in view of Pittman et al. (1994, *Biochemistry* 33: 6952-6959; reference AO

on 3/13/06 IDS), Bakker et al. (1994, *Journal of Biological Chemistry* 269: 20662-20667; reference U), and Ramabhadran (1994, *Pharmaceutical Design and* Development, Ellis Horwood, New York NY, pages 40, 42, and 43; reference V).

Hortin teaches that the complete sequence of human coagulation factor V (hereafter "Factor V") was known at the time of the invention and that said sequence includes the sequence DYDYQ (page 946, column 1, paragraph 2; and Figure 6 at page 950, e.g.). Hortin teaches that Factor V is sulfated *in vivo* suggests that the tyrosine residues at positions 696 and 698 are among the residues that are sulfated (page 950, column 2). Hortin speculates that thrombin binding to Factor V may be mediated by binding to these sites (page 951, column 1). Hortin teaches a solution comprising Factor V (page 946, column 2, last paragraph).

Hortin does not exemplify a peptide in which one or both of the tyrosines in the DYDY or DYDYQ motif are sulfated. Hortin does not teach any fragments of Factor V, e.g. the tetrapeptide DYDY or the pentapeptide DYDYQ.

Pittman teaches that inhibiting sulfation of Factor V inhibits its procoagulant activity (page 6955, column 1, under "Sulfation is required..."). Specifically, Pittman teaches that Factor V must be sulfated to undergo binding and subsequent cleavage by thrombin (page 6956, column 1; and Figure 3B). Pittman concurs with Hortin that tyrosines 696 and 698 are likely candidates for the sulfation (page 6957, column 1, under "Discussion"). Pittman also teaches methods for sulfating proteins (pages 6953 and 6954).

Bakker teaches that the portion of Factor V heavy chain required to bind thrombin is the C-terminal 27 amino acids thereof, which comprises the DYDYQ motif (see Table II at page 20665 and page 20664, column 1, first full paragraph). Bakker further teaches that these 27 amino acids are responsible for the binding of Factor V to prothrombin (page 20667, column 1, first full paragraph).

Ramabhadran teaches that small peptides (i.e., up to 50 amino acids) may be made in high yield and with high purity by synthesizing them chemically from their constituent amino acids (page 43). Ramabhadran teaches that chemically synthesized peptides are useful in the laboratory as drugs (page 43, third full paragraph).

A person of ordinary skill in the art would have had a reasonable expectation of success in sulfating either or both of the tyrosine residues at positions 696 and 698 within Factor V because Hortin and Pittman both teach that these residues are within consensus sequences for sulfation. The skilled artisan would have been motivated to sulfate one or both of these residues in Factor V because Pittman teaches that Factor V is not active unless it is sulfated.

The person of ordinary skill in the art would have had a further reasonable expectation of success in producing short peptides including tyrosine residues 696 and 698 because Hortin teaches that the entire sequence of Factor V was known at the time of the invention and because Ramabhadran teaches that peptides of up to 50 amino acids in length and with a given sequence may be chemically synthesized. The skilled artisan would have been motivated to produce such peptides because Bakker teaches that the C-terminal portion of Factor V heavy chain, which comprises tyrosine residues

696 and 698, is the domain required to bind prothrombin; the skilled artisan would have been motivated to determine which of these 27 residues is necessary for the interaction and which are not. Furthermore, sulfating these residues would have constituted routine experimentation on the part of the skilled artisan, since Pittman teaches methods for doing so. The skilled artisan would have been motivated to sulfate the tyrosine residues because Pittman and Horton both teach that they may be sulfated *in vivo*, because Bakker teaches that these residues are within a domain that binds prothrombin, and because Pittman teaches that Factor V must be sulfated to bind thrombin. Therefore, the skilled artisan would have endeavored to learn whether the tyrosine residues in the 27-amino acid peptide of Bakker need be sulfated to bind prothrombin. In light of the practical teachings and predictions of the art, the selection of the peptide sequence and sulfation pattern would have constituted routine experimentation at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The skilled artisan would have had a reasonable expectation that peptides made as suggested by the art as set forth above would inhibit thrombin activity because Hortin teaches that Factor V is bound and cleaved by thrombin, Bakker teaches that the C-terminal 27 amino acids of Factor V are the portion involved in binding thrombin, and Pittman and Horton teach that residues 696 and 698 are likely required for thrombin binding. See *KSR*.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to produce peptides using the method of Ramabhadran that correspond to various portions of the 27 amino acids of Factor V taught by Bakker

to be involved in binding thrombin in order to determine which portions of this fragment are necessary for thrombin binding. It would have been further obvious to sulfate one or more of the tyrosine residues within the resulting peptide because Pittman teaches that sulfation is required for activity and teaches methods for sulfating proteins.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651